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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,276	07/08/2003	Kristian DiMatteo	01194-458001 / 03-282	8211

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EXAMINER	
EBRAHIM, NABILA G	
ART UNIT	PAPER NUMBER
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/615,276	DIMATTEO ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15,17-27,29-33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-15, 17-27, 29-33, and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Applicant's remarks and amendments to the claims dated 11/17/2006 is acknowledged.

Status of Claims

Claims 1, 3-15, 17-27, 29-33, and 35-37 are pending in the application.

Claims 2, 16, 28, and 34 were cancelled.

Status of Office Action: Final

Information Disclosure Statement

In case that Applicant did not receive the initialed IDS, dated 7/15/2006 and 3/27/2006 an initialed copy is attached to this office action. An initialed copy–except for the duplicates- of the newly submitted IDS dated 11/17/2006 will be also mailed with this office action.

Claim Rejections - 35 USC § 112

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 8, and 10 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite an antibody selected from anti-PSMA, antibodies to CD20, antibodies to CD74, antibodies to CD52 antigens.....to the end of the claim, without any DEPOSIT INFORMATION.

The invention requires monoclonal antibodies like anti-PSMA, antibodies to CD20,..etc. Since the monoclonal antibodies are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. The specification does not disclose a repeatable process to obtain the recited antibodies and it is not apparent if the recited antibodies are readily available to the public. If these antibodies are not so obtainable or available, the requirements of 35 U.S.C. §112 may be satisfied by a deposit of each of these antibodies.

There is no indication in the specification as to the public availability of the recited antibodies. If a deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the different monoclonal antibody has been deposited under the Budapest Treaty and that the monoclonal antibodies will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit is not made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§1.801-1 .809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a. during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

b. all restrictions upon availability to the public will be irrevocably removed upon

granting of the patent;

c. the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

d. a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

e. the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. § 2400 in general, and specifically to §2411.05 , as well as to 37 C.F.R. § 1.809(d), Wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." Finally, Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection

10801 University Boulevard

Manassas, VA 20110-2209

2. In view of canceling claim 2 under 35 U.S.C. 112, second paragraph is herein withdrawn.

3. Claim 25 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. After amending, the claim recites, "the composition is

delivered by puncturing the skin and injecting the composition". Claim 21 recites the types of cancer conditions that the composition can be used with, as ovarian, colorectal, thyroid, gastrointestinal, breast, prostate, and lung cancers. The organs recited are not covered only by skin, it is not clear where the particles will be delivered, is it locally to the cancer site, or under the skin to reach the lesion indirectly through the blood.

Claim Rejections - 35 USC § 102

1. In view of the amendments of the claims, the rejection of claims 1, 3-6, 13-15, 17-24, 27, and 29-32 under 35 U.S.C. 102(b) as being anticipated by Chamberlain et al. (Br. J. Surg., Vol. 70 (1983), pages 596-598) is herein withdrawn.

2. In view of the amendments of the claims, the rejection of claims 1, 3-6, 13-15, 17- 24, 26, 27, and 29-32 under 35 U.S.C. 102 as being anticipated by Gray et al. PCT/AU2001/001370 (Gray) is herein withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-10, 13-15, 17- 24, 26, 27, and 29-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over either of Chamberlain et al. (Br. J. Surg., Vol. 70

(1983), pages 596-598) or Gray PCT/AU2001/001370 (Gray), in view of Kaminski et al US 6015542 (hereinafter Kaminski)

Chamberlain et al. disclose a physiological approach to treatment of hepatic metastases of malignant tumors wherein microspheres containing radioactive yttrium of 17 microns are delivered into the liver by the hepatic artery as a form of internally irradiating metastatic liver cancer, the disclosure means that the release of the radionuclide is restricted to the liver cells only. (see entire document, especially, summary, page 596). Chamberlain used the composition for treating cancer, the therapeutic agent of instant claim 3 is interpreted as any compound that is used in the treatment of an ailment or a disease. Accordingly, Chamberlain's compounds read on claim 3. In addition, the document discloses a method of preparation that comprises activated 90-yttrium is added to styrene-divinylbenzene copolymer ion exchange resin microspheres having diameter of 17.5+/-2 micrometers. The method comprises adding the Yttrium to copolymer ion exchange resin microspheres which result in a microsphere of specific density containing 10% Yttrium absorbed in the microsphere (page 579).

Gray discloses a particulate material having a diameter in the range of from 5 to 200 microns (page 6) comprising a polymeric matrix and stably incorporated radionuclide, such as radioactive yttrium (page 1), processes for its production and a method of radiation therapy utilizing the particulate material (abstract). Gray used the compound for treating cancer; the therapeutic agent of instant claim 3 is interpreted as any compound that is used in the treatment of an ailment or a disease. Accordingly,

Gray's compounds read also on claim 3. In addition, Gray disclosed that the radioisotope molecule is enclosed into the polymer bead (example 1). However, the method of preparation in example 1 does not exclude the possibility of having the drug on top of the polymer microspheres. The way of administration is by catheterization into the hepatic artery via the femoral, or brachial artery (page 8, lines 10+). One of the objectives of the invention is to decrease leaching of radionuclides from the polymeric matrix, which can cause non-specific radiation of the patient and damage surrounding tissue. The goal amount of leaching reaches less than 0.4% (page 5, lines 11+). Gray teaches a method of preparation, which comprises the step of adding colorless solution of yttrium (90Y) sulfate to symmetrical microspheres of ion exchange resin (example 1.)

Chamberlain and Gray are deficient in disclosing an antibody bound to the isotope.

Kaminski et al. teaches a radioactively labeled monoclonal antibody or radioactively labeled monoclonal antibody fragment wherein said antibody or said antibody fragment binds to CD20 antigen present on the surface of cells (claim 1), which can be labeled with a radioisotope (example III) is used to treat cancers (col. 9, lines 7+).

A skilled man in the art would have been motivated at the time the invention was made to label a monoclonal antibody with a radioisotope to advance the treatment of cancers.

4. Claims 1, 3-6, 11-15, 17- 24, 26, 27, and 29-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over either of Chamberlain or Gray in view of (Ajay, K. et

al. 1993, *Extended preoperative polyvinyl alcohol microembolization of intracranial meningiomas: assessment of two embolization techniques,* AJNR 14:571-582, May/Jun 1993) hereinafter "Ajay".

Chamberlain and Gray have been discussed above.

Chamberlain and Gray did not disclose polyvinyl alcohol as the particle polymer

Ajay evaluates the efficacy of preoperative meningioma devascularization with small polyvinyl alcohol (PVA) particles. The PVA particles are 150- to 300-microns.

It would have been obvious to one of ordinary skill in the art to use Polyvinyl particles as a carrier for a radioisotope which may be attached to an antibody and use it for other types of cancers like gastrointestinal, lung, thyroid, or breast cancers. The motivation would be the disclosed results of Ajay, which demonstrates that, the angiography after embolization demonstrated the total elimination of tumor blush in all patients.

Claims 1, 3-6, 13-15, 17- 24, 26, 27, and 29-32, 33, 35-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over either of Chamberlain or Gray in view of Atcher et al. US 4970062, hereinafter "Atcher".

Chamberlain and Gray are discussed above.

Chamberlain and Gray are deficient in disclosing the particle wherein the agent is attached to the surface of the particle.

Atcher teaches ferric hydroxide colloid having an alpha-emitting radionuclide essentially on the outer surfaces and a method of forming same. The method includes oxidizing a ferrous hydroxide to ferric hydroxide in the presence of a preselected

radionuclide to form a colloid having the radionuclide on the outer surface thereof, and thereafter washing the colloid, and suspending the washed colloid in a suitable solution. The labeled colloid is useful in cancer therapy and for the treatment of inflamed joints. A colloid is defined as a system in which finely divided particles, which are approximately 10 to 10,000 angstroms in size, are dispersed within a continuous medium in a manner that prevents them from being filtered easily or settled rapidly. Since Atcher describes a colloid, which is according to, the definition made of particles. It is understood that the radioisotope is attached to the outer surface of the particles (abstract).

Accordingly, it would have been obvious to one of ordinary skills in the art at the time the invention was made to develop a particle made of a polymer and attach the radionuclide because Atcher discloses that the surface attached radionuclides can be used in cancer therapy.

Claim 1, 3-6, 13-15, 17- 24, 26, and 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Chamberlain, or Gray in view of (Jo YW, 2001, *Use of Pharmasep Unit for Processing Microspheres*, AAPS PharmSciTech, March 31, 2001; 2 (1) Technical Note 2), hereinafter "Jo".

Chamberlain and Gray are discussed above.

Chamberlain and Gray are deficient in disclosing the distribution of pores in the particle.

Jo teaches microsphere technology for sustained delivery of therapeutic agents. The reference includes the use of PVA as a microsphere (see materials in page 2) and

explains how to control the pores density in a microsphere as having low and high porous mechanisms of production (methods of microsphere preparation page 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a sphere that includes different densities of porosities in one microsphere using different mechanisms of production because it is expected that once a method is known, it is within the skilled of a skilled man in the art to modify it to improve the product obtained by the method to further develop the sustained release of a drug.

Finally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to advance the compositions and the methods disclosed by either Chamberlain or Gray by using polyvinyl alcohol particles, an antibody for the type of cancer being treated, the radionuclide as attached to the surface of the particle as disclosed by Atcher, and the distribution of pores as disclosed by Jo for the reasons and motivations set forth above. It would have been further obvious to the skilled artisan to modify the methods and attach the radionuclide to the surface of the particle as disclosed by Atcher for the reasons and motivations set forth above. The expected results would be a composition used for gastrointestinal, and/or breast cancer therapy that comprise a polyvinyl polymer particle bound to a radionuclide, and an antibody. The radionuclide can be attached to the surface or encapsulated inside the polymer and the methods of production and use of the composition.

Response to Arguments

1. Applicant's arguments filed 11/17/2006 have been fully considered but they are not persuasive. **Applicant argues that:**

a. As amended, claims 8 and 10 cover anti-PSMA antibodies, and/or antibodies to CD20, CD74 and CD52 antigens, all of which are well-known and sequenced antigens. Therefore, a person having ordinary skill in the art would readily be able to obtain antibodies from a known antigen, as numerous well-established methods are available for obtaining antibodies. A monoclonal antibody can be obtained from the non-human animal and then modified using recombinant DNA techniques known in the art. Thus, Applicants believe that a deposit information is not necessary for the antibodies covered by claims 8 and 10, as amended. Applicants therefore request that this rejection be reconsidered and withdrawn.

To respond:

Applicant claims a monoclonal antibody, which needs a hyperdoma to be deposited, this is a requirement. Accordingly, rejection is maintained.

Applicant argues that:

b. Applicants amended claim 25 to obviate the rejection of this claim. Support for the amendment can be found, for example, at page 4, lines 10-11 of the specification. Therefore, Applicants request that this rejection be withdrawn.

To respond: The organs related to the cancers recited in claim 21 such as ovaries, colon, rectum, gastrointestinal system, and lung are not covered directly with skin which means that "puncturing the skin" will not lead the injection to reach the cancer lesion

unless the blood carries the composition to the site of the cancer. The claim remains indefinite.

Applicant argues that:

c. Neither Chamberlain nor Gray disclose particles with the specific porosity recited, and neither Wu, Welt, Ajay, Atcher, nor Jo, alone or in combination, cure Chamberlain's or Gray's infirmities, at least because neither Wu, Welt, Ajay, Atcher, nor Jo disclose or suggest particles including a first region including pores having a first predominant pore size and a second region surrounding the first region and including pores having a second predominant pore size, the first predominant pore size is larger than the second predominant pore size.

To respond:

As the office action demonstrates, Chamberlaim teaches microspheres containing radioactive yttrium of 17 microns, gray teaches a particulate material having a diameter in the range of from 5 to 200 microns comprising a polymeric matrix and stably incorporated radionuclide, such as radioactive yttrium, Kaminski discloses radioactively labeled monoclonal antibody or radioactively labeled monoclonal antibody fragment wherein said antibody or said antibody fragment binds to CD20 antigen, Atcher teaches Atcher teaches ferric hydroxide colloid having an alpha-emitting radionuclide essentially on the outer surfaces, Ajay teaches the preoperative meningioma devascularization with small polyvinyl alcohol (PVA) particles wherein the PVA particles are 150- to 300-microns, and Jo teaches microsphere technology for sustained delivery of therapeutic agents and explains how to control the pores density in

a microsphere as having low and high porous mechanisms of production which shows the importance of the different densities in delivering the active agent in an altered-release composition. The motivation is clear in the office action. Accordingly, a prima facie case of obviousness has been realized.

Conclusion

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nabila Ebrahim, M.D. 1/27/07

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER